Newborn Screening for Genetic and Endocrine Disorders (Screening, Medical Foods, and Treatment)

Clinical Preventive Service Recommendations

U.S. Preventive Services Task Force Recommendation

In 1996, the U.S. Preventive Services Task Force recommended screening newborns for phenylketonuria (PKU), congenital hypothyroidism (CH), and hemoglobin disorders.[1] It did not considered other disorders included in state newborn screening panels.

Given the availability of new evidence, the USPSTF has decided to update its 1996 recommendation on phenylketonuria (PKU). This review is currently underway. Please refer the USPSTF website for further information (www.ahrq.gov/clinic/uspstf/uspsspku.htm).

Other Recommended Guidance American Academy of Pediatrics (AAP)

The American Academy of Pediatrics (AAP) recommends that all food for special dietary use with accepted benefit for treatment of a medical condition be reimbursed [covered] as a medical expense, provided that the costs are over and above usual foods. All expenses for medical equipment and medical supplies necessary for the delivery of foods for special dietary use should be reimbursed [covered]. Reimbursement [coverage] for foods for special dietary use should be mandatory for the following[2]:

1. Any medical condition for which specific dietary components or the restriction of specific dietary components is necessary to treat a physical, physiologic, or pathologic condition resulting in inadequate nutrition.
2. An inherited metabolic disorder, including but not limited to disorders of carbohydrate metabolism, lipid metabolism, vitamin metabolism, mineral metabolism, or amino acid and nitrogen metabolism.
3. A condition resulting in impairment of oral intake that affects normal development and growth.

Evidence Rating:

Expert Consensus (Committee on Nutrition)

American College of Medical Genetics (ACMG)

An expert group convened by the American College of Medical Genetics (ACMG) with support from the Health Resources and Services Administration (HRSA) recently recommended a core panel of 29 disorders to be screened for in newborn blood spot specimens.[3] This screening panel has been endorsed by a Department of Health and Human Services (DHHS) Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children[4] and by professional organizations, including the American Academy of Pediatrics (AAP).[5]

PKU Management

Screening newborns is just a first step. In 2000, a NIH Consensus Statement on Phenylketonuria Screening and Management stated that a "multidisciplinary

approach to lifelong care…for the treatment of PKU with….continuity of care from infancy through adulthood is considered medically necessary for optimal outcomes for individuals with PKU." Treatment includes access to appropriate medical services at specialized multidisciplinary treatment centers and provision of medical formula and foods.[6]

SCD Management
NIH guidelines on the management of SCD, last revised in 2002, call for comprehensive management by a team that includes physicians, nurses, health educators, and medical social workers, as well as access to a number of specialists. NIH recommends that a mid-level practitioner coordinate preventive and primary care, pain management, transfusion and chelation therapy compliance, and education of patients and other health care providers.[7]

Information Sources

The recommendations and supporting information contained in this document came from several sources, including the:

- American Academy of Pediatrics (AAP)
- American College of Medical Genetics (ACMG)
- DHHS Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
- Government Accountability Office (GAO)
- National Institutes of Health (NIH)
- National Newborn Screening and Genetics Resource Center, funded by the Health Resources and Services Administration (HRSA)
- Peer-reviewed research

The background and supporting information contained in this document is a compilation of research findings. All information presented in this document should be attributed to its referenced source and should not be considered a reflection of other organizations cited in the text.

Condition/Disease Specific Information

Epidemiology of Condition/Disease

All states require that providers collect dried blood spot specimens from infants soon after birth and send them to be tested at an approved screening laboratory for a panel of disorders specified by the state. All states require screening for a minimum of four disorders: phenylketonuria (PKU), congenital hypothyroidism (CH), galactosemia, and sickle cell disease (SCD) and other hemoglobin disorders. Other disorders that are mandated by the majority of states include congenital adrenal hyperplasia (CAH), biotinidase deficiency, and medium chain acyl-CoA dehydrogenase (MCAD) deficiency.[8-9] Most states are moving to adopt the core panel of disorders recommended by the ACMG.

The most common newborn genetic disorders are congenital hypothyroidism (CH), with a prevalence at birth of 1 in 2,500 newborns, and sickle cell disease (SCD), which is diagnosed in 1 in 2,600 newborns.[9] The birth prevalence of phenylketonuria (PKU) in the United States is 1 in 20,000 newborns.

If untreated, phenylketonuria (PKU) results in severe mental retardation in most children. Congenital hypothyroidism (CH) results in mental retardation as well as other forms of cognitive impairment and physical and behavioral problems in many untreated infants. Sickle cell disease (SCD) results in repeated bouts of severe pain, disability, and can increase susceptibility to blood-borne infections that can cause sepsis, meningitis, and death. SCD also results in frequent, painful crises. In addition, children with SCD are at risk of stroke, which can cause brain damage and cognitive impairment.

Condition/Disease Risk Factors

Most disorders detected by newborn blood spot screening are genetic disorders, except for congenital hypothyroidism, an endocrine disorder which is primarily non-genetic.

Value of Prevention

Economic Burden of Condition/Disease

In the absence of screening and treatment, almost all children with phenylketonuria (PKU) (about 200 births per year) would develop mental retardation. The average *lifetime* direct and indirect cost per child born with mental retardation is $1 million (in year 2003 dollars).[10] This indicates a lifetime burden of at least $200 million for each birth cohort. Prior to screening, at least 1 in every 20,000 children developed mental retardation due to congenital hypothyroidism (CH).[11] This indicates that CH and PKU have similar economic burdens and, when combined, cost at least $400 million per year.

Sickle cell disease is a major cause of hospitalizations. During 1989 to 1993, hospitalization costs for children and adults with SCD averaged $475 million per year (in year) 1996 dollars.[12]

Workplace Burden of Condition/Disease

Family caregivers for children with disabling sequelae such as mental retardation or painful sickle cell crises are liable to miss days of work, cut back hours, or leave the workforce altogether. Mothers of children with disabling conditions are estimated to lose an average of approximately 5 hours of work per week, or 250 hours per year.[13] Assuming an hourly cost between $12 and $20 (including fringe benefits), that implies an economic cost from $3,000 to $5,000 per child, per year.[13]

Economic Benefit of Preventive Intervention

Screening for two disorders, phenylketonuria (PKU) and congenital hypothyroidism (CH), has been demonstrated to be cost-saving to public payers, with the averted costs of care exceeding the costs of providing screening and diagnostic services and treatment.[14]

Estimated Cost of Preventive Intervention

The cost of newborn screening for genetic and endocrine disorders depends on the conditions tested for, the screening instruments used, the number of specimens tested, and the type of follow-up conducted.[15]

A study by the General Accountability Office (GAO) concluded that, in 2001, state newborn screening programs spent over $120 million, or an average of $29.44 per infant.[16] All except 5 states charge a fee to birthing centers or other providers to cover the cost of providing laboratory screening and, to a varying

extent, follow-up services. Some states also use the fee to subsidize the costs of providing specialist services and/or medical foods. These fees vary from $10 to over $100 per infant.[17]

Estimated Cost of Treatment

Children with phenylketonuria (PKU) require treatment from specialized metabolic disease clinics. Dietary treatment for PKU, which is recommended for life, entails special phenylalanine-free formula that is supplemented with tyrosine and medical foods. The cost for one year of formula and medical foods can reach $10,000.[18] In contrast, congenital hypothyroidism (CH) can be treated by primary care providers using inexpensive thyroid hormone medications.

Children with sickle cell disease (SCD) may be prescribed antibiotics as prophylaxis against infections, and vaccination against selected bacterial infections may also be needed. Although many children with SCD are treated by primary care providers, outcomes such as survival are improved among children who receive care from a comprehensive SCD center.[19] Federally-insured children with SCD in 1992-1993 had mean expenditures 9 times higher than other similarly insured children.[20] Most of the costs were associated with hospital and emergency department admissions, although optimal pain management has been shown to reduce those costs substantially.[21] New interventions such as hydroxyurea, transfusions, and bone marrow transplantation offer promise in the prevention of painful crises, morbidity, disability, and mortality but, those treatments require significant expertise and specialized clinical experience to be utilized appropriately.[22]

Cost-Effectiveness and/or Cost-Benefit Analysis of Preventive Intervention

The cost-effectiveness of newborn screening is well established. In particular, screening for phenylketonuria (PKU) and congenital hypothyroidism (CH) is cost-saving, with the averted costs of care exceeding the costs of providing screening, diagnostic services, and treatment.[14] Screening for other disorders is generally cost-effective, if not cost-saving. For example, one analysis of screening for sickle cell disease (SCD) concluded that screening all newborns for SCD results in a cost of $10,000 per discounted life year saved.[23] Another analysis of newborn screening for medium chain acyl-CoA dehydrogenase (MCAD) deficiency found that the cost per quality-adjusted life year (QALY) is likely less than $30,000.[24]

Preventive Intervention Information

Preventive Intervention:

Newborn screening allows treatment to be initiated within the first few weeks of life thereby preventing some of the complications associated with genetic and endocrine disorders.

Purpose of Screening, Medical Foods, and Treatment

Newborn screening for phenylketonuria (PKU) and congenital hypothyroidism (CH) has been a major public health success in preventing numerous cases of intellectual disability and assuring normal development of thousands of children. Newborn screening for other disorders has saved the lives of many children who would otherwise have died in early childhood.

Benefits and Risks of Intervention

Studies have shown that treatment for phenylketonuria (PKU) and congenital hypothyroidism (CH), if begun in the first 3 weeks and adhered to subsequently,

can prevent mental retardation and assure normal cognitive functioning.[25-26] Risks resulting from discontinuation or lack of adherence to treatment vary with the age of the individual and the severity of the disorder. Newborn screening for sickle cell disease (SCD), in association with parent and provider education, clinical management, and vaccine and antibiotic prophylaxis, has been shown to prevent most deaths associated with SCD in the first 3 to 4 years of life. Early identification of SCD does not prevent pain crises and strokes, and long-term outcomes are less clear.[27] Treatments for other disorders that are included in some state screening panels also have benefits and risks. For example, a recent CDC report evaluated benefits and risks of screening and early treatment for cystic fibrosis.[28]

The effectiveness of newborn screening is dependent on access to appropriate medical services and treatments, including medical foods for disorders such as PKU. Failure of payers to cover medical foods can result in serious adverse consequences, including, for example, severe intellectual disability and devastating birth defects among children born to mothers with inadequately treated PKU.[29] Similarly, access to specialized, multidisciplinary treatment centers may be needed in order to minimize mortality and medical complications.

The main risk of screening is false-positive results, which can lead to unnecessary testing and unneeded treatment. False-negative screening results, as well as missed cases, may lead to delays in diagnosis and treatment.

Initiation, Cessation, and Interval of Screening, Medical Foods, and Treatment

Screening should be initiated upon birth, or as soon thereafter as possible, because initiation of treatment within the first few months of life may be required to prevent adverse outcomes. Some states require or recommend the collection of another blood spot specimen between 1 and 4 weeks of age. Families adopting children from other countries should consult their child's healthcare provider.

Medical foods and preventive treatment should be provided as medically necessary.

Intervention Process

A variety of types of equipment, reagents, and protocols are used to screen newborns. All newborn screening laboratories are CLIA-certified, use approved technologies, and participate in a rigorous proficiency testing and quality assurance program maintained by CDC in collaboration with the Association of Public Health Laboratories.

Children with positive screening test results need to be followed up with further testing. For disorders for which early treatment is urgent, treatment may be initiated based on presumptive positive results pending final confirmation.

Treatment Information

Children with genetic and endocrine disorders may require one or more of the following:

- Medical formula or medical foods
- Medications
- Treatment from specialized metabolic clinics

Health benefits should include provisions for case management services, access to

specialty clinics, medical formulas/foods, and medications — as medically indicated — for the purpose of preventing illness or disability among beneficiaries with genetic or endocrine disorders.

Strength of Evidence for the Clinical Preventive Service

The level of evidence supporting the recommendations contained in this section is described below.

Recommended Guidance:

Medical Foods
The American Academy of Pediatrics (AAP)
Strength of Evidence: Expert Consensus

- AAP recommends that all food for special dietary use with accepted benefit for treatment of a medical condition be reimbursed [covered] as a medical expense, provided that the costs are over and above usual foods. All expenses for medical equipment and medical supplies necessary for the delivery of foods for special dietary use should be reimbursed [covered].[2]

Screening
American College of Medical Genetics (ACMG)
Strength of Evidence: Expert Opinion

- An expert group convened by the American College of Medical Genetics (ACMG) recently recommended a core panel of 29 disorders to be screened for in newborn blood spot specimens.[3]

Management and Preventive Medication
National Institutes on Health (NIH)
Strength of Evidence: Not Specified

- NIH PKU treatment guidelines stipulate that treatment should include access to appropriate medical services at specialized multidisciplinary treatment centers and provision of medical formula and foods.[6]
- NIH guidelines on the management of SCD call for comprehensive management by a team that comprises doctors, nurses, health educators, and medical social workers, as well as access to a number of specialties. The NIH recommends coordination of care by a mid-level practitioner, including preventive and primary care, pain management, transfusion and chelation therapy compliance, and education of patients and other health care providers.[7]

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